IN THE CLAIMS:

1. (Currently Amended) A biosensor comprising:

(a) a two-dimensional grating;

(b) a substrate that supports the two-dimensional grating; wherein the refractive index of the two-dimensional grating is greater than the refractive index of the substrate; and

(c) one or more specific binding substances immobilized on the surface of the two-dimensional grating opposite of the substrate layer; wherein the one or more specific binding substances are bound to their binding partners and wherein one or more specific binding substances and their binding partners are detection label-free wherein, when the biosensor is illuminated a resonant grating effect is produced on ~~the~~ a reflected radiation spectrum, and wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect.

2. (Original) The biosensor of claim 1, wherein a narrow band of optical wavelengths is reflected from the biosensor when the biosensor is illuminated with a broad band of optical wavelengths.

3. (Original) The biosensor of claim 1, wherein the substrate comprises glass, plastic or epoxy.

4. (Original) The biosensor of claim 1, wherein the two-dimensional grating is comprised of a material selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide, and silicon nitride.

5. (Previously Presented) The biosensor of claim 1, further comprising a cover layer on the surface of the two-dimensional grating opposite of the substrate, wherein the one or more specific binding substances are immobilized on the surface of the cover layer opposite of the two-dimensional grating.

6. (Previously Presented) The biosensor of claim 5, wherein the cover layer comprises a material that has a lower refractive index than zinc sulfide, titanium dioxide, tantalum oxide, or silicon nitride.

7. (Original) The biosensor of claim 6, wherein the cover layer comprises a material selected from the group consisting of glass, epoxy, and plastic.

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8. (Original) The biosensor of claim 1, wherein the two-dimensional grating has a period of about 0.01 microns to about 1 micron and a depth of about 0.01 microns to about 1 micron.

9. (Original) The biosensor of claim 1, wherein the one or more specific binding substances are arranged in an array of distinct locations.

10. (Original) The biosensor of claim 1, wherein the one or more specific binding substances are immobilized on the two-dimensional grating by physical adsorption or by chemical binding.

11. (Original) The biosensor of claim 9, wherein the distinct locations define a microarray spot of about 50-500 microns in diameter.

12. (Canceled)

13. (Original) The biosensor of claim 1, wherein the one or more specific binding substances are selected from the group consisting of nucleic acids, polypeptides, antigens, polyclonal antibodies, monoclonal antibodies, single chain antibodies (scFv), F(ab) fragments, $F(ab')_2$ fragments, Fv fragments, small organic molecules, cells, viruses, bacteria, and biological samples.

14. (Original) The biosensor of claim 13, wherein the biological sample is selected from the group consisting of blood, plasma, serum, gastrointestinal secretions, homogenates of tissues or tumors, synovial fluid, feces, saliva, sputum, cyst fluid, amniotic fluid, cerebrospinal fluid, peritoneal fluid, lung lavage fluid, semen, lymphatic fluid, tears, and prostatitc fluid.

15. (Original) The biosensor of claim 12, wherein the binding partners are selected from the group consisting of nucleic acids, polypeptides, antigens, polyclonal antibodies, monoclonal antibodies, single chain antibodies (scFv), F(ab) fragments, $F(ab')_2$ fragments, Fv fragments, small organic molecules, cells, viruses, bacteria, and biological samples.

16. (Original) The biosensor of claim 15, wherein the biological sample is selected from the group consisting of blood, plasma, serum, gastrointestinal secretions, homogenates of tissues or tumors, synovial fluid, feces, saliva, sputum, cyst fluid, amniotic fluid,

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cerebrospinal fluid, peritoneal fluid, lung lavage fluid, semen, lymphatic fluid, tears, and prostatitc fluid.

17. (Original) A liquid-containing vessel comprising the biosensor of claim 1 as an internal surface.

18. (Original) The liquid-containing vessel of claim 17, wherein the vessel is selected from the group consisting of a microtiter plate, a test tube, a petri dish and a microfluidic channel.

19. (Original) A detection system comprising the biosensor of claim 1, a light source that directs light to the biosensor, and a detector that detects light reflected from the biosensor, wherein a polarizing filter occurs between the light source and the biosensor.

20. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

(a) applying one or more binding partners to the biosensor of claim 1;

(b) illuminating the biosensor with light; and

(c) detecting a maxima in reflected wavelength, or a minima in transmitted wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

21. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

(a) applying one or more binding partners to the biosensor of claim 1, wherein the two-dimensional grating is coated with an array of distinct locations containing the one or more specific binding substances;

(b) illuminating each distinct location of the biosensor with light; and

(c) detecting maximum reflected wavelength or minimum transmitted wavelength of light from each distinct location of the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners at a distinct location, then the reflected wavelength of light is shifted.

22. (Withdrawn) A method of detecting activity of an enzyme comprising:

(a) applying one or more enzymes to the biosensor of claim 1;

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(b) washing the biosensor;

(c) illuminating the biosensor with light; and

(d) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more enzymes have altered the one or more specific binding substances of the biosensor by enzymatic activity, then the reflected wavelength of light is shifted.

23. (Withdrawn) A biosensor comprising:

(a) a sheet material having a first and second surface, wherein the first surface defines relief volume diffraction structures;

(b) a reflective material coated onto the first surface of the sheet material; and

(c) one or more specific binding substances immobilized on the reflective material; wherein the biosensor reflects light predominantly at a first single optical wavelength when illuminated with a broad band of optical wavelengths, and wherein the biosensor reflects light at a second single optical wavelength when the one or more specific binding substances are immobilized on the reflective surface, wherein the reflection at the second optical wavelength of light results from optical interference.

24. (Withdrawn) The biosensor of claim 23, wherein the biosensor reflects light at a third single optical wavelength when the one or more specific binding substances are bound to their respective binding partners, wherein the reflection at the third optical wavelength results from optical interference.

25. (Withdrawn) The biosensor of claim 23, wherein the depth and period of the relief volume diffraction structures are less than the resonance wavelength of the light reflected from the biosensor.

26. (Withdrawn) The biosensor of claim 23, wherein the relief volume diffraction structures have a period of about 0.01 microns to about 1 micron and a depth of about 0.01 micron to about 1 micron.

27. (Withdrawn) The biosensor of claim 23, wherein the one or more specific binding substances are bound to their respective binding partners.

28. (Withdrawn) A liquid-containing vessel comprising the biosensor of claim 23 as an internal surface.

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29. (Withdrawn) The liquid-containing vessel of claim 28, wherein the vessel is selected from the group consisting of a microtiter plate, a test tube, a petri dish and a microfluidic channel.

30. (Withdrawn) The biosensor of claim 23, wherein the one or more specific binding substances are arranged in an array of distinct locations on the reflective material.

31. (Withdrawn) The biosensor of claim 30, wherein the distinct locations define a microarray spot of about 50-500 microns in diameter.

32. (Withdrawn) The biosensor of claim 23, wherein the one or more specific binding substances are immobilized to the reflective material by physical adsorption or by chemical binding.

33. (Withdrawn) The biosensor of claim 32, wherein the relief volume diffraction structures are about 0.5 microns to about 5 microns in diameter.

34. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

(a) applying one or more binding partners to the biosensor of claim 23;

(b) illuminating the biosensor with light; and

(c) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

35. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

(a) applying one or more binding partners to the biosensor of claim 23, wherein the one or more specific binding substances are arranged in an array of distinct locations on the reflective material;

(b) illuminating each distinct location of the biosensor with light; and

(c) detecting reflected wavelength of light from each distinct location of the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners at a distinct location, then the reflected wavelength of light is shifted.

36. (Withdrawn) A method of detecting activity of an enzyme comprising:

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(a) applying one or more enzymes to the biosensor of claim 23;

(b) washing the biosensor;

(c) illuminating the biosensor with light; and

(d) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more enzymes have altered the one or more specific binding substances of the biosensor by enzymatic activity, then the reflected wavelength of light is shifted.

37. (Withdrawn) A biosensor comprising a two-dimensional grating having a first and a second surface comprised of an optically transparent material that conducts electricity, wherein the first surface of the two-dimensional grating is coated with an electrical insulator, and wherein the second surface of the two-dimensional grating is deposited on a substrate, wherein when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and the period of the two-dimensional grating are less than the wavelength of the resonant grating effect.

38. (Withdrawn) The biosensor of claim 37, wherein the two-dimensional grating is comprised of a repeating pattern of shapes selected from the group consisting of squares, circles, ellipses, triangles, ovals, trapezoids, sinusoidal waves, rectangles, and hexagons.

39. (Withdrawn) The biosensor of claim 37, wherein the repeating pattern of shapes are arranged in a rectangular grid or hexagonal grid.

40. (Withdrawn) The biosensor of claim 37, wherein the two-dimensional grating has a period of about 0.01 microns to about 1 micron and a depth of about 0.01 microns to about 1 micron.

41. (Withdrawn) The biosensor of claim 37, wherein two or more separate grating regions are present on the same substrate.

42. (Withdrawn) The biosensor of claim 41, further comprising an electrically conducting trace to each separate grating region of the substrate.

43. (Withdrawn) The biosensor of claim 42, wherein the conducting trace is connected to a voltage source.

44. (Withdrawn) The biosensor of claim 41, wherein one or more specific binding substances are bound to each separate grating region of the substrate.

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45. (Withdrawn) The biosensor of claim 44, wherein the one or more specific binding substances are bound to their respective binding partners.

46. (Withdrawn) A liquid-containing vessel comprising the biosensor of claim 37 as an internal surface.

47. (Withdrawn) The liquid-containing vessel of claim 46, wherein the vessel is selected from the group consisting of a microtiter plate, a test tube, a petri dish and a microfluidic channel.

48. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

(a) applying one or more binding partners to the biosensor of claim 37;

(b) applying an electrical charge to the electrically conducting traces;

(c) illuminating the biosensor with light; and

(d) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

49. (Withdrawn) The method of claim 48, further comprising the step of applying a reversed electrical charge to the electrically conducting traces before illuminating the biosensor with light.

50. (Withdrawn) A method of measuring the amount of one or more binding partners in a test sample comprising:

(a) illuminating the biosensor of claims 1, 23, or 37 with light;

(b) detecting reflected wavelength of light from the biosensor;

(d) applying a test sample comprising one or more binding partners to the biosensor;

(e) illuminating the biosensor with light; and

(f) detecting reflected wavelength of light from the biosensor;

wherein, the difference in wavelength of light in step (b) and step (f) is a measurement of the amount of one or more binding partners in the test sample.

51. (Currently Amended) A detection system comprising the biosensor of claim 1, a light source that directs light at the biosensor, and a detector that detects light reflected from the biosensor, wherein a first fiber probe, which is ~~an illuminating~~ a collecting fiber

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probe, having two ends is connected at its first end to the detector, wherein a second fiber probe, which is ~~a collection~~ an illuminating fiber probe, having two ends is connected at its first end to the light source, wherein the first and second fiber probes are connected at their second ends to a third fiber probe, wherein the third fiber probe acts as an illumination and collection fiber probe, and wherein the third fiber probe is oriented at a normal angle of incidence to the biosensor and supports counter-propagating illuminating and reflecting optical signals.

52. (Previously Presented) A detection system comprising the biosensor of claim 1, a light source that directs light at the biosensor, and a detector that detects light reflected from the biosensor, wherein an illuminating fiber probe is connected to the light source and is oriented at a 90 degree angle to a collecting fiber probe, wherein the collecting fiber probe is connected to the detector, wherein light is directed through the illuminating fiber probe into a beam splitter that directs the light to the biosensor, wherein reflected light is directed into the beam splitter that directs the light into the collecting fiber.

53. (Withdrawn) A method of immobilizing one or more specific binding substances onto the biosensor of claim 1, 23, or 37 comprising activating the biosensor with amine, attaching linker groups to the amine-activated biosensor, and attaching one or more specific binding substances to the linker groups.

54. (Withdrawn) The method of claim 53, wherein the biosensor is activated with amine by a method comprising:

(a) immersing the biosensor into a piranha solution;

(b) washing the biosensor;

(c) immersing the biosensor in 3% 3-aminopropyltriethoxysilane solution in dry acetone;

(d) washing the biosensor in dry acetone; and

(e) washing the biosensor with water.

55. (Withdrawn) The method of claim 53, wherein the linker is selected from the group consisting of amine; aldehyde; N, N'-disuccinimidyl carbonate; and nickel.

56. (Withdrawn)A method of detecting the binding of one or more specific binding substances to their respective binding partners comprising:

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(a) applying one or more binding partners comprising one or more tags to the biosensor of claims 1, 23, or 37;

(b) illuminating the biosensor with light; and

(c) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

57. (Withdrawn) The method of claim 56, wherein the one or more tags are selected from the group consisting of biotin, succinimidyl-6-[a-methyl-a-(2-pyridyl-dithio) toluamido] hexanoate (SMPT), dimethylpimelimidate (DMP), and histidine.

58. (Withdrawn) The method of claim 56, wherein the one or more tags are reacted with a composition selected from the group consisting of streptavidin, horseradish peroxidase, and streptavidin coated nanoparticles, before the step of illuminating the biosensor with light.

59. (Previously Presented) A biosensor composition comprising two or more biosensors of claim 9 wherein the biosensors are associated with a holding fixture.

60. (Original) The biosensor composition of claim 59, wherein the composition comprises about 50 to about 1,000 individual biosensors.

61. (Original) The biosensor composition of claim 59, wherein the composition comprises about 96 biosensors.

62. (Original) The biosensor composition of claim 59, wherein the composition comprises about 384 biosensors.

63. (Original) The biosensor composition of claim 59, wherein the two or more biosensors each comprise about 25 to about 1,000 distinct locations.

64. (Original) The biosensor composition of claim 59, wherein each biosensor is about 1 mm^2 to about 5 mm^2.

65. (Original) The biosensor composition of claim 59, wherein each biosensor is about 3 mm^2.

66. (Original) The biosensor composition of claim 59, wherein the holding fixture holds each biosensor such that each biosensor can be placed into a separate well of a microtiter plate.

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67. (Previously Presented) A biosensor composition comprising one or more biosensors of claim 1 on a tip of a multi-fiber optic probe.

68. (Previously Presented) The biosensor composition of claim 67, wherein the one or more biosensors are fabricated on the tip of the probe.

69. (Original) The biosensor composition of claim 67, wherein the one or more biosensors are attached onto the tip of the probe.

70. (Withdrawn) A method of detecting binding of one or more specific binding substances to their respective binding partners *in vivo* comprising:

(a) inserting the tip of the fiber optic probe of claim 67 into the body of a human or animal;

(b) illuminating the biosensor with light;

(c) detecting reflected wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

71. (Original) A detection system comprising:

(a) the biosensor of claim 1;

(b) a laser source that directs a laser beam to a scanning mirror device, wherein the scanning mirror device is used to vary the laser beam's incident angle;

(c) an optical system for maintaining columination of the incident laser beam;

(d) and a light detector.

72. (Original) The detection system of claim 71, wherein the scanning mirror device is a linear galvanometer.

73. (Original) The detection system of claim 72, wherein the linear galvanometer operates at a frequency of about 2 Hz to about 120 Hz and a mechanical scan angle of about 10 degrees to about 20 degrees.

74. (Original) The detection system of claim 71, wherein the laser is a diode laser with a wavelength selected from the group consisting of 780 nm, 785 nm, 810 nm, and 830 nm.

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75. (Withdrawn) A method for determining a location of a resonant peak for a binding partner in a resonant reflectance spectrum with a colorimetric resonant biosensor, comprising:

selecting a set of resonant reflectance data for a plurality of colormetric resonant biosensor distinct locations,

wherein the set of resonant reflectance data is collected by illuminating a colormetric resonant diffractive grating surface with a light source and measuring reflected light at a pre-determined incidence,

wherein the colormetric resonant diffractive grating surface is used as a

surface binding platform for one or more specific binding substances,

wherein binding partners can be detected without use of a molecular label,

wherein the set of resonant reflectance data includes a plurality of sets of two measurements, where a first measurement includes a first reflectance spectra of one or more specific binding substances that are attached to the colormetric resonant diffractive grating surface and a second measurement includes a second reflectance spectra of the one or more specific binding substance after one or more binding partners are applied to colormetric resonant diffractive grating surface including the one or more specific binding substances, and

wherein a difference in a peak wavelength between the first and second measurement is a measurement of an amount of binding partners that bound to the one or more specific binding substances;

determining a maximum value for a second measurement from the plurality of sets of two measurements from the set of resonant reflectance data for the plurality of binding partners, wherein the maximum value includes inherent noise included in the resonant reflectance data;

determining whether the maximum value is greater than a pre-determined threshold, and if so,

defining a curve-fit region around the determined maximum value,

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performing a curve-fitting procedure to fit a curve around the curve-fit region, wherein the curve-fitting procedure removes a pre-determined amount of inherent noise included in the resonant reflectance data;

determining a location of a maximum resonant peak on the fitted curve; and

determining a value of the maximum resonant peak, wherein the value of the maximum resonant peak is used to identify an amount of biomolecular binding of the one or more specific binding substances to the one or more binding partners.

76. (Withdrawn) A computer readable medium having stored therein instructions for causing a processor to execute the method of claim 75.

77. (Withdrawn) The method of claim 75 wherein a sensitivity of a colormetric resonant biosensor is determined by a shift in a location of a resonant peak in the plurality of sets of two measurements in the set of resonant reflectance data.

78. (Withdrawn) The method of claim 75 wherein the step of selecting a set of resonant reflectance data includes selecting a set of resonant reflectance data:

x_i and y_i for i = 1, 2, 3, ...n,

wherein x_i is where a first measurement includes a first reflectance spectra of one or more specific binding substance attached to the colormetric resonant diffractive grating surface, y_i a second measurement includes a second reflectance spectra of the one or more specific binding substances after a plurality of binding partners are applied to colormetric resonant diffractive grating surface including the one or more specific binding substances, and n is a total number of measurements collected.

79. (Withdrawn) The method of claim 75 wherein the step of determining a maximum value for a second measurement includes determining a maximum value y_k such that:

$(y_k >= y_i)$ for all $i \neq k$.

80. (Withdrawn) The method of claim 75 wherein the step of determining whether the maximum value is greater than a pre-determined threshold includes:

computing a mean of the set of resonant reflectance data;

computing a standard deviation of the set of resonant reflectance data; and

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determining whether ((y_k – mean)/standard deviation) is greater than a pre-determined threshold.

81. (Withdrawn) The method of claim 75 wherein the step of defining a curve-fit region around the determined maximum value includes:

defining a curve-fit region of (2w+1) bins, wherein w is a pre-determined accuracy value;

extracting ($x_{i,}$, k –w <= i <= k + w); and

extracting ($y_{i,}$, k – w <= i <= k + w).

82. (Withdrawn) The method of claim 75 wherein the step of performing a curve-fitting procedure includes:

computing $g_i = \ln y_i$;

performing a 2^{nd} order polynomial fit on g_i to obtain g'_i defined on

($x_{i,}$, k –w <= i <= k + w);

determining from the 2^{nd} order polynomial fit coefficients a, b and c of for (ax^2 + bx +c)-; and

computing $y'_i = e^{g'i}$.

83. (Withdrawn) The method of claim 75 wherein the step of determining a location of a maximum resonant peak on the fitted curve includes:

determining location of maximum resonant peak (x_p = (-b)/2a).

84. (Withdrawn) The method of claim 75, wherein the step of determining a value of the maximum resonant peak includes determining the value with of x_p at y'_p.

85. (Withdrawn) A biosensor comprising a two-dimensional grating having a pattern of concentric rings, wherein the difference between an inside diameter and an outside diameter of each concentric ring is equal to about one-half of a grating period, wherein each successive ring has an inside diameter that is about one grating period greater than an inside diameter of a previous ring wherein when the structure is illuminated with an illuminating light beam, a reflected radiation spectrum is produced that is independent of an illumination polarization angle of the illuminating light beam, and wherein one or more specific binding substances are immobilized on the two-dimensional grating.

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86. (Withdrawn) The biosensor of claim 85, wherein when the structure is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect, and wherein a narrow band of optical wavelengths is reflected from the structure when the structure is illuminated with a broadband of optical wavelengths.

87. (Withdrawn) The biosensor of claim 85, wherein the two-dimensional grating has a period of about 0.01 microns to about 1 micron and a depth of about 0.01 microns to about 1 micron.

88. (Withdrawn) A biosensor comprising an array of holes or posts arranged such that the holes or posts are centered on corners and in the center of hexagons, wherein the hexagons are arranged in a closely packed array, wherein when the structure is illuminated with an illuminating light beam, a reflected radiation spectrum is produced that is independent of an illumination polarization angle of the illuminating light beam, and wherein one or more specific binding substances are immobilized on the array of holes or posts.

89. (Withdrawn) The biosensor of claim 88, wherein when the structure is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth or height and period of the holes or posts are less than the wavelength of the resonant grating effect, and wherein a narrow band of optical wavelengths is reflected from the structure when the structure is illuminated with a broad band of optical wavelengths.

90. (Withdrawn) The structure of claim 88, wherein the array holes or posts have a period of about 0.01 microns to about 1 micron and a depth of height of about 0.01 microns to about 1 micron.

91. (Withdrawn) A biosensor comprising:

(a) a first two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface;

(b) a second two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface, wherein the top surface of the

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second two-dimensional grating is attached to the bottom surface of the first two-dimensional grating; and

(c) one or more specific binding substances or one or more specific binding substances bound to their binding partners immobilized on the top surface of the first two-dimensional grating;

wherein, when the biosensor is illuminated two resonant grating effects are produced on the reflected radiation spectrum, and wherein the depth and period of both of the two-dimensional gratings are less than the wavelength of the resonant grating effects.

92. (Withdrawn) The biosensor of claim 91, wherein a substrate layer supports the bottom surface of the second two-dimensional grating.

93. (Withdrawn) The biosensor of claim 91, further comprising a cover layer on the top surface of the first two-dimensional grating, wherein the one or more specific binding substances are immobilized on the surface of the cover layer opposite of the two-dimensional grating.

94. (Withdrawn) The biosensor of claim 91, wherein the top surface of the first two-dimensional grating is in physical contact with a test sample, and the second two dimensional grating is not in physical contact with the test sample.

95. (Withdrawn) The biosensor of claim 91, wherein when a peak resonant reflection wavelength is measured for the first and second two-dimensional gratings, the difference between the two measurements indicates the amount of one or more specific binding substances, binding partners, or both deposited on the surface of the first two-dimensional grating.

96. (Withdrawn) A biosensor comprising:

(a) a first two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface;

(b) a substrate layer comprising a top surface and a bottom surface, wherein the top surface of the substrate supports the bottom surface of the first two-dimensional grating;

(c) a second two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface, wherein the bottom surface of the second two-dimensional grating is attached to the bottom surface of the substrate; and

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(d) one or more specific binding substances or one or more specific binding substances bound to their binding partners immobilized on the top surface of the first two-dimensional grating;

wherein, when the biosensor is illuminated two resonant grating effects are produced on the reflected radiation spectrum, and wherein the depth and period of both of the two-dimensional gratings are less than the wavelength of the resonant grating effects.

97. (Withdrawn) The biosensor of claim 96, further comprising a cover layer on the top surface of the first two-dimensional grating, wherein the one or more specific binding substances are immobilized on the surface of the cover layer opposite of the two-dimensional grating.

98. (Withdrawn) The biosensor of claim 96, wherein the top surface of the first two-dimensional grating is in physical contact with a test sample, and the second two dimensional grating is not in physical contact with the test sample.

99. (Withdrawn) The biosensor of claim 98, wherein when a peak resonant reflection wavelength is measured for the first and second two-dimensional gratings, the difference between the two measurements indicates the amount of one or more specific binding substances, binding partners, or both deposited on the surface of the first two-dimensional grating.

100. (Original) The biosensor of claim 1, further comprising an antireflective dielectric coating on a surface of the substrate opposite of the two-dimensional grating.

101. (Previously Presented) The biosensor of claim 1, wherein the biosensor is attached to a bottomless microtiter plate.

102. (Withdrawn) A method of detecting an interaction of a first molecule with a second test molecule comprising:

(a) applying a mixture of the first and second molecules to a distinct location on a biosensor, wherein the biosensor comprises a two-dimensional grating comprising of a high refractive index material, and a substrate layer that supports the two-dimensional grating; and wherein, when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum, and wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect;

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(b) applying a mixture of the first molecule with a third control molecule to a distinct location on the biosensor of (a) or a similar biosensor, wherein the third control molecule does not interact with the first molecule, and wherein the third control molecule is about the same size as the first molecule; and

(c) detecting a shift in the reflected wavelength of light from the distinct locations of step (a) and step (b);

wherein, if the shift in the reflected wavelength of light from the distinct location of step (a) is greater than the shift in the reflected wavelength in step (b), then the first molecule and the second test molecule interact.

103. (Withdrawn) The method of claim 102, wherein the first molecule is selected from the group consisting of a nucleic acid, polypeptide, antigen, polyclonal antibody, monoclonal antibody, single chain antibody (scFv), F(ab) fragment, $F(ab')_2$ fragment, Fv fragment, small organic molecule, cell, virus, and bacteria.

104. (Withdrawn) The method of claim 102, wherein the second test molecule is selected from the group consisting of a nucleic acid, polypeptide, antigen, polyclonal antibody, monoclonal antibody, single chain antibody (scFv), F(ab) fragment, $F(ab')_2$ fragment, Fv fragment, small organic molecule, cell, virus, and bacteria.

105. (Withdrawn) A biosensor comprising:

(a) a two-dimensional grating comprised of a material having a high refractive index; and

(b) a substrate layer that supports the two-dimensional grating;

wherein, the grating is amine activated, aldehyde activated, or nickel activated, wherein when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum, and wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect.

106. (Withdrawn) A biosensor comprising a two-dimensional grating having a pattern of concentric rings, wherein the difference between an inside diameter and an outside diameter of each concentric ring is equal to about one-half of a grating period, wherein each successive ring has an inside diameter that is about one grating period greater than an inside diameter of a previous ring, wherein when the structure is

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illuminated with an illuminating light beam, a reflected radiation spectrum is produced that is independent of an illumination polarization angle of the illuminating light beam, and wherein the grating is amine activated, aldehyde activated, or nickel activated.

107. (Withdrawn) A biosensor comprising an array of holes or posts arranged such that the holes or posts are centered on corners and in the center of hexagons, wherein the hexagons are arranged in a closely packed array, wherein when the structure is illuminated with an illuminating light beam, a reflected radiation spectrum is produced that is independent of an illumination polarization angle of the illuminating light beam, and wherein the grating is amine activated, aldehyde activated, or nickel activated.

108. (Withdrawn) A biosensor comprising:

(a) a first two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface; and

(b) a second two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface, wherein the top surface of the second two-dimensional grating is attached to the bottom surface of the first two-dimensional grating; wherein the top surface of the first two-dimensional grating is amine activated, aldehyde activated, or nickel activated; wherein when the biosensor is illuminated two resonant grating effects are produced on the reflected radiation spectrum, and wherein the depth and period of both of the two-dimensional gratings are less than the wavelength of the resonant grating effects.

109. (Withdrawn) A biosensor comprising:

(a) a first two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface;

(b) a substrate layer comprising a top surface and a bottom surface, wherein the top surface of the substrate supports the bottom surface of the first two-dimensional grating; and

(c) a second two-dimensional grating comprising a high refractive index material and having a top surface and a bottom surface, wherein the bottom surface of the second two-dimensional grating is attached to the bottom surface of the substrate;

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wherein the top surface of the first two-dimensional grating is amine activated, aldehyde activated, or nickel activated; wherein when the biosensor is illuminated two resonant grating effects are produced on the reflected radiation spectrum; and wherein the depth and period of both of the two-dimensional gratings are less than the wavelength of the resonant grating effects.

110. (Currently Amended) An array of polynucleotides comprising:

(a) a two-dimensional grating;

(b) a substrate that supports the two-dimensional grating; wherein the refractive index of the two-dimensional grating is greater than the refractive index of the substrate; and

(c) one or more types of polynucleotides attached at distinct locations of the two-dimensional grating opposite the substrate; wherein the one or more polynucleotides are bound to one or more specific binding substances, and wherein the one or more polynucleotides and the one or more specific binding substances are detection label-free;

wherein, when the array of polynucleotides is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and period of the two-dimensional grating are less than the resonant grating effect wavelength~~, and wherein the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the two-dimensional grating produces a detectable change in the resonant grating effect on the reflected radiation spectrum~~.

111. (Previously Presented) The array of polynucleotides of claim 110, wherein a narrow band of optical wavelengths is reflected from the array when the array is illuminated with a broad band of optical wavelengths.

112. (Previously Presented) The array of polynucleotides of claim 110, wherein the substrate comprises glass, plastic or epoxy.

113. (Previously Presented) The array of polynucleotides of claim 110, wherein the two-dimensional grating is comprised of a material selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide and silicon nitride.

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114. (Previously Presented) The array of polynucleotides of claim 110, wherein the substrate and the two-dimensional grating comprise a single unit, wherein the surface of the single unit comprising the two-dimensional grating is coated with a material having a refractive index that is greater than the refractive index of the substrate;

115. (Previously Presented) The array of polynucleotides of claim 114, wherein the single unit is comprised of a material selected from the group consisting of glass, plastic and epoxy.

116. (Previously Presented) The array of polynucleotides of claim 114, wherein the material is selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide and silicon nitride.

117. (Previously Presented) The array of polynucleotides of claim 110, wherein the two-dimensional grating is comprised of a repeating pattern of shapes selected from the group consisting of squares, circles, ellipses, triangles, trapezoids, sinusoidal waves, ovals, rectangles and hexagons.

118. (Previously Presented) The array of polynucleotides of claim 117, wherein the repeating pattern of shapes are arranged in a rectangular grid or hexagonal grid.

119. (Previously Presented) The array of polynucleotides of claim 110, wherein the two-dimensional grating has a period of about 0.01 microns to about 1 micron and a depth of about 0.01 microns to about 1 micron.

120. (Previously Presented) The array of polynucleotides of claim 110, further comprising an antireflective physical structure that is embossed into a surface of the substrate opposite of the two-dimensional grating.

121. (Previously Presented) The array of polynucleotides of claim 120, wherein the antireflective physical structure is a motheye structure.

122. (Previously Presented) A detection system comprising the array of polynucleotides of claim 110, a light source that directs light to the array of polynucleotides, and a detector that detects light reflected from the array of polynucleotides.

123. (Previously Presented) The detection system of claim 122, further comprising a fiber probe comprising one or more illuminating optical fibers that are connected at a first

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end to the light source, and one or more collecting optical fibers connected at a first end to the detector, wherein the second ends of the illuminating and collecting fibers are arranged in line with a collimating lens that focuses light onto the array of polynucleotides.

124. (Previously Presented) The detection system of claim 123, wherein the illuminating fiber and the collecting fiber are the same fiber.

125. (Previously Presented) The detection system of claim 122, wherein the light source illuminates the array of polynucleotides from its top surface or from its bottom surface.

126. (Withdrawn) An array of polynucleotides comprising:

(a) a sheet material having a first and second surface, wherein the first surface defines relief volume diffraction structures; and

(b) a reflective material coated onto the first surface of the sheet material;

(c) one or more types of polynucleotides attached at distinct locations to the reflective material;

wherein the array of polynucleotides is capable of reflecting light predominantly at a first single optical wavelength when illuminated with a broad band of optical wavelengths as a result of optical interference, and wherein binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the reflective material produces a detectable change in the wavelength of reflected light.

127. (Withdrawn) The array of polynucleotides of claim 126, further comprising a light source that directs light to the reflective surface and a detector that detects light reflected from the reflective surface.

128. (Withdrawn) The array of polynucleotides of claim 126, wherein the relief volume diffraction structures are about 0.5 microns to about 5 microns in diameter.

129. (Currently Amended) An array of polynucleotides comprising:

(a) a two-dimensional grating;

(b) a substrate that supports the two-dimensional grating; wherein the refractive index of the two-dimensional grating is greater than the refractive index of the substrate; and

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(c) a cover layer on a surface of the two-dimensional grating opposite of the substrate;

(d) one or more types of polynucleotides attached at distinct locations to the cover layer,

(e) wherein the one or more types of polynucleotides are bound to their binding partners and wherein the one or more types of polynucleotides and their binding partners are detection label-free,

wherein, when the array is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and period of the two-dimensional grating are less than the resonant grating effect wavelength~~, and wherein binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations to the cover layer produces a detectable change in the resonant grating effect on the reflected radiation spectrum~~.

130. (Previously Presented) The array of polynucleotides of claim 129, wherein a narrow band of optical wavelengths is reflected from the optical device when the array is illuminated with a broad band of optical wavelengths.

131. (Previously Presented) The array of polynucleotides of claim 129, wherein the substrate comprises glass, plastic or epoxy.

132. (Previously Presented) The array of polynucleotides of claim 129, wherein the two-dimensional grating is comprised of a material selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide and silicon nitride.

133. (Previously Presented) The array of polynucleotides of claim 129, wherein the substrate and the two-dimensional grating comprise a single unit, wherein the surface of the single unit comprising the two-dimensional grating is coated with a material having a refractive index greater than the refractive index of the substrate and the material is coated with a cover layer.

134. (Previously Presented) The array of polynucleotides of claim 133, wherein the single unit is comprised of a material selected from the group consisting of glass, plastic, and epoxy.

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135. (Previously Presented) The array of polynucleotides of claim 133, wherein the material is selected from the group consisting of zinc sulfide, titanium dioxide, tantalum oxide and silicon nitride.

136. (Previously Presented) The array of polynucleotides of claim 129, wherein the cover layer comprises a material that has a lower refractive index than zinc sulfide, titanium dioxide, tantalum oxide or silicon nitride.

137. (Previously Presented) The array of polynucleotides of claim 136, wherein the cover layer comprises a material selected from the group consisting of glass, epoxy and plastic.

138. (Previously Presented) The array of polynucleotides of claim 129, wherein the two-dimensional grating is comprised of a repeating pattern of shapes selected from the group consisting of squares, circles, ellipses, triangles, trapezoids, sinusoidal waves, ovals, rectangles and hexagons.

139. (Previously Presented) The array of polynucleotides of claim 138, wherein the repeating pattern of shapes are arranged in a rectangular grid or hexagonal grid.

140. (Previously Presented) The array of polynucleotides of claim 129, wherein the two-dimensional grating has a period of about 0.01 microns to about 1 micron and a depth of about 0.01 microns to about 1 micron.

141. (Previously Presented) The array of polynucleotides of claim 129, further comprising an antireflective physical structure that is embossed into a surface of the substrate opposite of the two-dimensional grating.

142. (Previously Presented) The array of polynucleotides of claim 141, wherein the antireflective physical structure is a motheye structure.

143. (Previously Presented) A detection system comprising the array of polynucleotides of claim 129, a light source that directs light to the array of polynucleotides, and a detector that detects light reflected from the array of polynucleotides.

144. (Previously Presented) The detection system of claim 143, further comprising a fiber probe comprising one or more illuminating optical fibers that are connected at a first end to the light source, and one or more collecting optical fibers connected at a first end

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to the detector, wherein the second ends of the illuminating and collecting fibers are arranged in line with a collimating lens that focuses light onto the array of polynucleotides.

145. (Previously Presented) The detection system of claim 144, wherein the illuminating fiber and the collecting fiber are the same fiber.

146. (Previously Presented) The detection system of claim 143, wherein the light source illuminates the array of polynucleotides from its top surface or from its bottom surface.

147. (Withdrawn) An array of polynucleotides device comprising:

(a) a sheet material having a first and second surface, wherein the first surface defines relief volume diffraction structures; and

(b) a reflective material coated onto the first surface of the sheet material;

(c) a cover layer on the surface of the reflective material coated onto the first surface of the sheet material;

(d) one or more types of polynucleotides attached at distinct locations to the cover layer,

wherein the array of polynucleotides is capable of reflecting light predominantly at a first single optical wavelength when illuminated with a broad band of optical wavelengths as a result of optical interference, and wherein the binding of a specific binding substance to the one or more types of polynucleotides attached at distinct locations of the cover layer produces a detectable change in the wavelength of reflected light.

148. (Withdrawn) The array of polynucleotides of claim 147, further comprising a light source that directs light to the reflective surface and a detector that detects light reflected from the reflective surface.

149. (Withdrawn) The array of polynucleotides of claim 147, wherein the relief volume diffraction structures are about 0.5 microns to about 5 microns in diameter.

150. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective unlabeled binding partners comprising:

(a) applying one or more unlabeled binding partners to a biosensor comprising:

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(1) a two-dimensional grating comprised of a material having a high refractive index;

(2) a substrate layer that supports the two-dimensional grating; and

(3) one or more specific binding substances immobilized on the surface of the two-dimensional grating opposite of the substrate layer; wherein, when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum, and wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect;

(b) illuminating the biosensor with light; and

(c) detecting a maxima in reflected wavelength, or a minima in transmitted wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective binding partners, then the reflected wavelength of light is shifted.

151. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective unlabeled binding partners comprising:

(a) applying one or more unlabeled binding partners to a biosensor comprising

(1) a two-dimensional grating comprised of a material having a high refractive index;

(2) a substrate layer that supports the two-dimensional grating; and

(3) one or more specific binding substances immobilized on a surface of the two-dimensional grating opposite of the substrate layer; wherein, when the biosensor is illuminated a resonant grating effect is produced on the reflected radiation spectrum, wherein the depth and period of the two-dimensional grating are less than the wavelength of the resonant grating effect, and wherein the two-dimensional grating is coated with an array of distinct locations containing the one or more specific binding substances;

(b) illuminating each distinct location of the biosensor with light; and

(c) detecting maximum reflected wavelength or minimum transmitted wavelength of light from each distinct location of the biosensor;

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wherein, if the one or more specific binding substances have bound to their respective unlabeled binding partners at a distinct location, then the reflected wavelength of light is shifted.

152. (Withdrawn) A method of detecting binding of one or more specific binding substances to their respective unlabeled binding partners comprising:

(a) illuminating a surface-relief volume diffractive structures (SRVD) biosensor with light and detecting reflected wavelength of light from the biosensor;

(b) applying one or more unlabeled binding partners to the SRVD biosensor;

(c) illuminating the biosensor with light and detecting reflected wavelength of light from the biosensor;

wherein, if the one or more specific binding substances have bound to their respective unlabeled binding partners, then the reflected wavelength of light is shifted.

153. (Withdrawn) A method of detecting the binding of one or more specific binding substances to their respective unlabeled binding partners comprising:

(a) illuminating a SRVD biosensor with light and detecting reflected wavelength of light from the biosensor;

(b) applying one or more unlabeled binding partners to the SRVD biosensor, wherein the one or more specific binding substances are arranged in an array of distinct locations on the SRVD biosensor;

(c) illuminating each distinct location of the SRVD biosensor with light and detecting reflected wavelength of light from each distinct location of the SRVD biosensor;

wherein, if the one or more specific binding substances have bound to their respective unlabeled binding partners at a distinct location, then the reflected wavelength of light is shifted.

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